General

Guideline Title

Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition).

Bibliographic Source(s)

Collins PW, Chalmers E, Hart DP, Liesner R, Rangarajan S, Talks K, Williams M, Hay CR, UK Haemophilia Centre Doctors. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. Br J Haematol. 2013 Jan;160(2):153-70. PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Hay CR, Brown S, Collins PW, Keeling DM, Liesner R. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the UK Haemophilia Centre Doctors Organisation (UKHCDO). Br J Haematol 2006;133:591–605.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A-C) and strength of recommendation (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Risk Factors for Inhibitor Formation

- Factor VIII/IX (FVIII/FIX) mutation analysis should be undertaken in all patients with haemophilia A and B, especially newly diagnosed patients (2C).
- Previously untreated and minimally treated patients with severe haemophilia A who have received an intensive FVIII exposure (≥5 exposure days [EDs]) should be closely monitored for inhibitor formation (1B). Some consideration may be given to starting early prophylaxis (2C).
- All patients who require replacement therapy with concentrate, including previously untreated patients, should be treated with recombinant FVIII/IX (1C).

Diagnosis and Investigation of Factor VIII and IX Inhibitors

- An inhibitor test should be performed in severely affected patients with haemophilia A or B at least every third ED or every 3 months until the 20th ED (2C). After the 20th ED an inhibitor test should be done every 3-6 months up to 150 EDs. For haemophilia A, inhibitor testing should continue 1 to 2 times a year indefinitely (1C). For haemophilia B, testing after 150 EDs is only required if clinically indicated.
- An inhibitor test should be performed in all patients with haemophilia A before any change in concentrate and at least twice in the first 6

months after the change or if there is any change in bleeding pattern or response to FVIII (2C).

- An inhibitor test should be performed in mild and moderate haemophilia A yearly (if they have been exposed to FVIII) or after intensive exposure (≥5 EDs) or after surgery (1C).
- Patients with mild/moderate haemophilia A and a mutation with high inhibitor prevalence and/or family history of inhibitors should undergo inhibitor testing after all exposures (1C).
- Patients with haemophilia B should be tested after an allergic reaction to replacement therapy before any further FIX exposure occurs (1B).
- Tests to detect the presence or titre of an inhibitor should be done after a washout that ensures that the baseline factor level has been reached (1B).
- With currently available methodology it is difficult to accurately monitor FVIII half-life in patients with low titre inhibitors in routine clinical practice. If required, half-life should be measured by the methods described in the International Immune Tolerance study (2C). The current consensus definition for a FVIII inhibitor is an elimination half-life of <6 h, but this is likely to be an underestimate (2B) and the definition suggested in this guideline is <7 h (2B).
- The guideline developers suggest that a pragmatic and clinically relevant surrogate measure of normal pharmacokinetics is a FVIII level ≥1 iu/dl at 48 h in an individual receiving standard prophylaxis (20-50 iu/kg on alternate days) (2C).
- There is no criterion for recognition of a FIX inhibitor other than the presence of a positive Bethesda assay (2C).
- *In vivo* recovery (IVR) is a relatively inaccurate method to assess the strength of an inhibitor but is useful for guiding replacement therapy (2B).

Treatment of Inhibitors

Immune Tolerance Induction

- Immune toleration induction (ITI) is recommended for patients with severe haemophilia A and a persistent inhibitor that interferes with prophylaxis or treatment of bleeds at standard doses of FVIII (1B).
- The probability of good ITI outcome may be estimated using the peak historical inhibitor titre and starting titre (good-risk: <200 and <10 Bethesda units (BU)/ml, respectively) (1C).
- ITI should be started as soon as possible after the inhibitor has been confirmed and when the titre is <10 BU/ml (1B).
- If the inhibitor titre is >10 BU/ml at diagnosis, the start of ITI should be deferred until it has fallen below 10 BU/ml (1B). If this has not happened after 1 year, consideration should be given to commencing ITI (2C).
- If the historic peak inhibitor titre is <5 BU/ml, ITI should be started at a dose of 50 iu/kg on alternate days (2B).
- If the starting inhibitor titre is <10 BU/ml and the historic peak <200 BU/ml ITI should commence with 100 iu/kg/d unless peak is <5 BU/ml (see above) (2B).
- If the starting inhibitor titre is >10 BU/ml or the historic peak >200 BU/ml ITI should commence with 200 iu/kg/d (2B).
- If the ITI regimen of 50 iu/kg alternate days or 100 iu/kg/d is complicated by bleeding episodes the dose should be increased in stages up to 200 iu/kg/d to control bleeds (2B).
- ITI should continue as long as there is a convincing downward trend in inhibitor titre (20% in a 6 month period after the peak inhibitor titre has been reached) and interruptions in ITI should be avoided (2C).
- Dose tapering may be considered in good risk patients once the post-washout Bethesda titre is negative on two consecutive occasions and the 24-h FVIII trough level is ≥1 iu/dl. The FVIII dose should be reduced whilst maintaining a 24-h trough level ≥1 iu/dl and minimizing break-through bleeds (2C).
- Once the FVIII dose has been reduced to ≤50 iu/kg on alternate days whilst maintaining a trough FVIII level ≥1 iu/dl or the FVIII half-life after a washout is >7 h, the patient can be considered tolerant (2C).
- If there is an inadequate decrease in the inhibitor titre (20% reduction over a 6-month period) an alternative strategy may be considered. Options include FVIII dose increase, the introduction of plasma-derived factor VIII (pdFVIII), immunosuppression with rituximab, or stopping ITI (2C). If there is no adequate response within 6 months after introduction of second-line therapy ITI should be stopped (2C).
- Careful consideration should be given to attempting to induce immune tolerance in patients with haemophilia B, given the relatively poor response rate and risk of anaphylaxis and the nephrotic syndrome. Successful tolerization has been reported and the addition of immunosuppression to the ITI has been associated with the highest success rates (2C).
- In patients with mild/moderate haemophilia A and an inhibitor, a trial of on-demand bypassing therapy should precede consideration of ITI, the success rate of which is low in this group. (1C).
- In patients with mild/moderate haemophilia A and an inhibitor associated with a bleeding phenotype similar to acquired haemophilia A, a trial of immunosuppression should be considered (2C).
- ITI should be conducted under the supervision of a Haemophilia Comprehensive Care Centre (CCC) with expertise in inhibitor treatment, as defined by the National Service Specification. (1C).

Treatment of Specific Bleeding Problems

- Arrangements should be in place to treat bleeds within 2 h, either at home or in hospital. Patients should be on home treatment with agreed initial regimens as soon as is practically possible, combined with arrangements for rapid access to hospital review and or advice from an experienced clinician (2C).
- Bleeds may be managed with large doses of FVIII/IX in low responders and FVIII inhibitor bypassing activity (FEIBA) or activated recombinant FVII (rFVIIa) in high responders. FVIII can be considered for major bleeds in high responding patients with low-titre antibodies. For low-responding patients with low-titre inhibitors it is better to increase the frequency of FVIII/FIX infusions rather than increase the dose (2C).
- Patients who have experienced allergic reactions to FIX should be treated with rFVIIa (1C).
- Single dose FEIBA (50-100 μg/kg), single high dose (270 μg/kg) rFVIIa or 1-3 standard doses (90 μg/kg) of rFVIIa are all treatment options for early haemarthroses (1B).
- Treatment of non-joint bleeds should be with FVIII/FIX or standard doses of FEIBA or rFVIIa until further data are available (2C).
- Tranexamic acid should be considered in all patients who are not receiving high doses of FEIBA (>200 iu/kg/d) but is especially important for mucosal bleeds (2C).
- Some bleeds, unresponsive to bypassing agents, may be successfully treated by removal of the inhibitor using plasmaphaeresis and immunoadsorption together with high dose FVIII/IX concentrate (2B).
- Combined treatment with rFVIIa and FEIBA should only be considered for life- or limb-threatening bleeds unresponsive to either agent used alone (2C).
- Patients with mild/moderate haemophilia A with high inhibitor prevalence mutations or family history of inhibitor, should be treated with desmopressin (DDAVP) wherever possible to avoid FVIII exposure (1C).
- Patients with mild/moderate haemophilia A and an inhibitor should have a DDAVP trial, including a 4-h fall off FVIII level and this agent, combined with tranexamic acid, should be used whenever possible to avoid FVIII exposure (2C).
- Management of a bleed depends on its site and severity, knowledge of the inhibitor titre and previous response to bypassing agents and whether the patient is a low or high responder (2C).

Surgery

- Surgery in patients with inhibitors should be conducted at a CCC with experience in surgery in inhibitor patients and 24-h specialist consultant cover (1C). Haemostasis cannot be guaranteed with any available haemostatic agent, therefore, surgical procedures should be undertaken only after a careful assessment of the potential risks and benefits (1B).
- FVIII/IX can be used if satisfactory plasma levels can be achieved (1C).
- rFVIIa or FEIBA can be used at recommended licensed doses (2C). If the original bypassing therapy fails, then the alternate bypass agent may be used.

Prophylaxis for Inhibitor Patients

- Prophylaxis with a bypassing agent should be considered in young children after the first haemarthosis to reduce the risk of arthropathy (2C).
- If prophylaxis is required in patients awaiting ITI, rFVIIa should be used (2C).
- Prophylaxis with bypassing agents in patients on ITI should undergo a trial reduction when FVIII recovery is measureable and stopped when the Bethesda titre is negative, assuming significant break-through bleeds do not result (2C).
- Prophylaxis may be considered in older patients with recurrent bleeds or progressive arthropathy (2C).
- The choice of product for prophylaxis should be considered on an individual basis, taking into account previous response to treatment, logistics of administration and cost (2C).
- If the initial regimen is unsuccessful, increasing the frequency of infusion is more likely to be effective than increasing the dose (2C).

Monitoring Bypassing Agents

- The use of laboratory tests to monitor and determine dose of bypassing agent therapy in patients with inhibitors is not recommended outside of clinical trials (2C).

Definitions:

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Congenital haemophilia

Guideline Category

Assessment of Therapeutic Effectiveness

Diagnosis

Management

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Hematology

Internal Medicine

Medical Genetics

Pharmacology

Surgery

Intended Users

Physician Assistants

Physicians

Guideline Objective(s)

To provide healthcare professionals in the United Kingdom with pragmatic guidance on the management of patients with factor VIII/IX (FVIII/FIX) inhibitors, although individual patient circumstances may dictate an alternative approach

Target Population

Patients with congenital haemophilia (mild, moderate, severe) and possible factor VIII/IX (FVIII/FIX) inhibitor development

Interventions and Practices Considered

Diagnosis/Risk Assessment

1. Factor VIII/IX (FVIII/FIX) mutation analysis
2. Monitoring for inhibitor formation
3. Inhibitor testing

Treatment/Management

1. Recombinant FVIII/FIX
2. FVIII *in vivo* recovery (IVR)
3. Immune toleration induction (ITI) under supervision of a Haemophilia Comprehensive Care Centre (CCC)
4. Alternative strategies
    - FVIII dose increase
    - Plasma-derived (pd) FVIII introduction
    - Immunosuppression with rituximab
    - Stopping ITI
5. Bleed management
    - Large doses of FVIII/IX
    - FVIII inhibitor bypassing activity (FEIBA)
    - Activated recombinant FVII (rFVIIa)
    - Tranexamic acid
    - Plasmapheresis and immunoadsorption
    - Desmopressin (DDAVP)
6. Surgery at a CCC
7. Prophylaxis

Note: Use of laboratory tests to monitor and determine dose of bypassing agent therapy in patients with inhibitors is not recommended outside of clinical trials.

Major Outcomes Considered

- Immune tolerance
- Inhibitor formation
- Bleeding problems
- Haemostasis
- Quality of life

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The writing group reviewed publications known to them supplemented with papers identified through PubMed, using index terms h(a)emophilia, factor VIII and IX, inhibitors, alloantibodies, rFVIIa, NovoSeven, FEIBA, aPCC, rituximab, management. The search covered articles published from 2005 to 2012.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

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(A) High: Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate: Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low: Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to quote levels and grades of evidence,

details of which can be found in the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The writing group produced the draft guideline, which was reviewed and revised by members of the United Kingdom Haemophilia Centre Doctors Organization (UKHCDO) Advisory Board.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The guideline was reviewed by a sounding board of approximately 50 United Kingdom (UK) haematologists, the British Committee for Standards in Haematology (BCSH), and the British Society for Haematology Committees and comments incorporated where appropriate.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Accurate diagnosis and appropriate treatment of factor VIII/IX (FVIII/FIX) inhibitors in congenital haemophilia

Potential Harms

- Patients receiving bypassing agents are at risk of thrombosis, particularly adults with associated co-morbidities, and should be regularly monitored clinically for such events.
- There is a risk of patient relapse after immune tolerance induction (ITI) therapy.
- The authors are aware of unpublished venous thrombotic events associated with combined treatment with activated recombinant factor VII (rFVIIa) and factor VIII (FVIII) inhibitor bypassing activity (FEIBA) and this should only be considered for life- or limb-threatening bleeds unresponsive to either agent used alone.
- Concerns about concomitant use of tranexamic acid with FEIBA exist but reports of complications are very rare.

Qualifying Statements

Qualifying Statements

- These guidelines are targeted towards haemophilia treaters in the United Kingdom (UK). Not all recommendations may be appropriate for other countries with different health care arrangements and resources.
- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the United Kingdom Haemophilia Centre Doctors Organization (UKHCDO), the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

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Collins PW, Chalmers E, Hart DP, Liesner R, Rangarajan S, Talks K, Williams M, Hay CR, UK Haemophilia Centre Doctors. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). UK Haemophilia Centre Doctors Organization. Br J Haematol. 2013 Jan;160(2):153-70. PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Jan

Guideline Developer(s)

British Committee for Standards in Haematology - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

British Committee for Standards in Haematology (BCSH) Writing Group

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

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Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on August 7, 2013. The information was verified by the guideline developer on September 4, 2013. This summary was updated by ECRI Institute on November 21, 2013 following the U.S. Food and Drug Administration advisory on Arzerra (ofatumumab) and Rituxan (rituximab).

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